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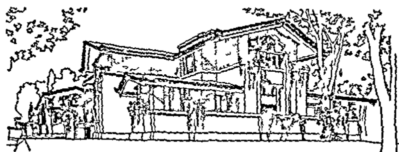
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The Pathologic Physiology of UREMIA in Chronic Bright's Disease

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INTRODUCTION

DYSFUNCTION of the kidney due to local structural damage is the essential and primary cause of uremia in chronic Bright s disease However renal dysfunction *per se* provokes few symptoms directly Rather it tends to operate in an indirect manner by changing first the composition of the plasma and in turn the chemical structure and the volume of the other body fluids The resulting disturbances interfere with the metabolism and function of many other organs and eventually cause symptoms Thus derangement may occur consecutively or simultaneously in several systems the renal circulatory central nervous gastro-intestinal skeletal and finally in the body as a whole *It is the purpose of this lecture to survey and correlate the various functional disorders with the clinical manifestations of uremia*

DEFINITIONS

At the outset we are faced with the necessity of clarifying certain terms and concepts upon which the following discussion is hinged Of these the more important are uremia and chronic Bright s disease Unfortunately neither expression has attained a definitive or widely accepted meaning This is only to be expected in view of constant changes in our ideas due to improvements of methodology and the accumulation of new factual data In a general sense agreement does exist among most physicians concerning clinical concepts of these conditions but ideas of their pathologic physiology and chemistry are vague and ill defined

Renal Insufficiency and Uremia

There are many renal insufficiencies A failure to maintain acid base balance to conserve salt to excrete nitrogen each of these and many others separately or in combination constitute insufficiency of renal function But in general usage the term becomes more inclusive and applies to any failure of the kidney to play its role efficiently in regulating the composition of plasma A diagnosis of renal insufficiency, then becomes at first a matter of biochemistry Symptomatology may or may not appear

The term uremia has been used for a century to denote the symptom complex resulting from renal insufficiency (1) Much confusion has arisen in its use in part because the biochemical abnormalities have always been obscure and in part because the uremic syndrome has been redefined in the light of additional facts Since it was believed in 1840 that retention of urine was the chief source of difficulty a word meaning literally urine in the blood was suggested as a satisfactory label It is now apparent that this theory of etiology is inadequate since uri

nary *losses* of water and electrolytes may frequently have a larger part in causing symptoms than retention

Certain symptoms of what was at first called uremia are now known to be caused by arterial hypertension Thus convulsions and other neurological manifestations once considered to be an integral part of uremia have been shown to be largely attributable to hypertensive disease, which may cause so called pseudo uremia or hypertensive encephalopathy independently of renal insufficiency (2 3) Hypertensive encephalopathy may vary widely in character from minor transient localized manifestations of cerebral irritation, such as parathesiae to generalized convulsions, that may prove fatal Less frequently, aphasia, dysphasia or palsies of varying extent and duration may develop Such episodes are to be differentiated from those due to renal retention of toxic agents to depletion of substances essential to the maintenance of normal neuromuscular irritability or to defects in water balance causing cerebral edema Convulsions occur in less than five per cent of patients with uremia when hypertension is absent (3) Other neurologic disorders are also uncommon

Soon after Bright (4) pointed out the relationship between renal damage and dropsy, it was discovered that nitrogen retention occurred in chronic renal disease Exhaustive chemical studies have since been made and it is now clear that the chemical anatomy of the plasma undergoes profound alteration during uremia Consequently uremia has acquired a biochemical connotation in addition to its clinical meaning Indeed some students of the disorder consider this to be its more important aspect (5), since the clinical pattern is so diverse and irregular Thus while recognizing that rare instances of advanced renal insufficiency may occur without obvious nitrogen retention, they have come to regard azotemia as a distinctive feature of uremia

Many prefer to restrict the use of the term uremia to cases in which intrinsic, structural renal disease is responsible, denoting manifestations based on functional disturbances by some other term Thus, prerenal azotemia or extra renal uremia, are used

to signify that renal function is impaired by interference with the renal circulation as in shock dehydration chronic anemia or heart failure The term postrenal azotemia is sometimes employed in preference to uremia, when renal insufficiency arises from obstruction to urinary outflow in the absence of renal damage Since uremia has nearly always been defined as a clinical syndrome it seems illogical to refer to the same symptom complex by different names especially when the underlying physiological changes are so often similar For this reason uremia will be used in this lecture to denote the clinical picture associated with azotemia caused by renal insufficiency whatever its origin

Chronic Bright s Disease

For many years the nature of the renal diseases described by Richard Bright in 1827 has provided material for controversy Bright delineated three varieties and suggested that possibly more than one disease was involved in producing the various pathologic changes he observed Others took the view that a single disease process was responsible but as facts have accumulated the pluralistic view has gained strength and it is now generally accepted These conditions are properly referred to as the chronic diseases of Bright designating the specific disease concerned in any given case However the older term remains in use because it denotes a constellation of disorders that are often impossible to differentiate

Bright s diseases may be divided into three main groups *the nephritides the nephroses and the nephroscleroses* Glomerulonephritis and pyelonephrities are the most important members of the *first group* They are similar in producing the contracted granular kidney of chronic Bright s disease by inflammatory destruction associated with extensive fibrosis over a long period of time They differ in etiology and in initial pathology *The nephroses* comprise a heterogenous group of disorders that as yet defy logical and satisfactory classification Many of these entities such as intercapillary glomerulosclerosis protracted renal amyloidosis, or se

vere necrotizing nephrosis due to heavy metal poisoning, shock, or the crush syndrome, ultimately may cause chronic uremia The hypertensive diseases of the kidney, or *nephroscleroses*, are less likely to result in renal insufficiency Benign nephrosclerosis may rarely do so whereas malignant nephrosclerosis characteristically is associated with renal failure The familiar statement that ten per cent of patients with essential hypertension die in uremia is misleading since this group of fatalities is comprised almost entirely of patients with malignant nephrosclerosis

Initially, renal lesions may affect predominantly either the interstitium the vasculature, the glomeruli or the tubules depending upon the etiology, but with progression all structures are so disorganized and deformed that definitive pathological diagnosis may be impossible Glomerulonephritis, for example is at first characterized by glomerular damage, with interference of filtration by thickening of capillary basement membranes, intraglomerular exudation and capillary occlusion Later, nephron destruction thickening and distortion of the vascular bed and extensive fibrosis result in marked alteration of the structure and functions of the rest of the kidney Hypertensive disease on the other hand at first produces vascular pathology with resultant local hemodynamic changes Ultimately tissue necrosis and replacement fibrosis develop as a result of the extensive arteriolosclerosis and severe ischemia While at the beginning certain activities, such as blood flow, glomerular filtration or tubular function may be preponderantly disturbed in each in time the early specific patterns of pathology and physiology tend to merge into a single, non specific terminal state At this stage, glomerulonephritis and nephrosclerosis may be *indistinguishable It is often* convenient to allude to the final common stage (usually associated with uremia and hypertension) as chronic Bright s disease particularly when a *specific diagnosis is uncertain or impossible*

THE RENAL PHYSIOLOGY OF UREMIA IN CHRONIC BRIGHTS DISEASE

MANY DISCRETE but closely interrelated renal operations are concerned in the process of regulating the composition of the plasma These operations are dependent upon normal blood flow through the kidneys adequate filtration in the glomeruli and functional integrity of the tubular cells The formation of filtrate is primarily a vascular function subject to cardiovascular control The filtrate itself and the conduits through which it flows may be considered respectively as a modification of the blood and an extension of the circulatory system The blood filtrate is further modified by tubular activity so as to prevent excessive loss of water and electrolytes and to promote efficient disposal of metabolic wastes It is evident that cardiovascular disorders quite apart from renal parenchymal disease may seriously disturb these intricate and closely integrated processes Such disorders may be, and often are operative during the course of renal disease Glomerular filtration and tubular activity are likewise interdependent The tubules cannot function without filtrate and filtration without adequate tubular function may result in a rapid loss of body water and eventually in death

RENAL BLOOD FLOW

In normal man the renal blood flow averages 1200 ml per minute or approximately one quarter of the cardiac output (6) Removal of the renal circuit without cardiovascular adjustment would increase the total peripheral vascular resistance and the mean arterial pressure by one third Moreover, 1200 ml of blood would become available for the perfusion of other circuits Consequently the renal circulation can and does take an active part in circulatory hemostasis Vasoconstriction in the kidney can divert blood to areas where it may be urgently required such as to the heart and brain during peripheral vascular collapse (7) or other

conditions when the effective circulating blood volume is reduced (8, 9) This activity appears to take precedence over functions designed primarily to maintain the chemical structure and volume of body fluids

Glomerular filtration, the *sine qua non* of urine formation, depends upon a normal relationship between blood flow and pressure in the glomerular capillaries Disturbance of this relationship as a result either of vascular adjustments or structural change, will lead to abnormal filtration and to various biochemical derangements

Data now available on the behavior of the renal blood flow in health and disease in man are largely based on indirect measurements In animals many methods of measuring renal blood flow have found use, but most of them must be condemned as unphysiologic and as inapplicable in man because of the traumatic operative procedures required (10) The clearance concept has resolved this difficulty Any substance removed from the blood by the kidney and excreted in the urine may be said to be cleared completely from a volume of blood defined by dividing the amount of the substance in each milliliter of blood entering the kidney into the total amount appearing in the urine each minute (UV/B when U is the concentration in each milliliter of urine, V the urine flow per minute in milliliters and B the concentrtaion in each milliliter of blood) With most substances this volume is virtual rather than actual, but when the blood flowing through the kidney is cleared completely of any substance, the clearance figure equals the volume of blood flow per minute No substance could yield a higher clearance value unless it were simultaneously manufactured by the kidney A search for an appropriate substance has revealed that diodrast yields maximal clearance values (6) More recently sodium p aminohippurate has been found to have an equally high clearance (11 12) It is noteworthy that both substances have identical clearances indicating that each measures the same volume of blood

It should be emphasized that the use of the clearance method

entails the assumption that the test material is extracted by the kidney from all the blood perfusing it This, of course is unlikely since a certain percentage of blood does not perfuse extracting tissue but flows through the capsular connective tissue the calyces and the pelves where no tubular tissue is present For this reason the diodrast and p aminohippurate clearances are said to measure the *effective* renal plasma flow (13) Recent work has validated this usage

The percentage of diodrast or p aminohippurate extracted from the blood flowing through the kidney can be determined by measuring the relative concentrations of these substances in the arterial blood entering and the venous blood leaving the kidney The first is obtained by arterial puncture and the second by catheterizing the renal vein both relatively simple procedures In venous catheterization a long radio-opaque ureteral catheter specially made for the purpose is passed into an antecubital vein thence through the axillary vein superior vena cava and the right atrium under fluoroscopic control It then may be passed into the inferior vena cava and *right* renal vein Clotting of blood in the catheter is prevented by instilling normal saline solution slowly through the catheter Blood may be withdrawn as desired

In twenty normal human subjects the renal extraction of p-aminohippurate averaged 92 5 per cent Others have obtained a somewhat lower figure in a smaller series of cases (14) The discrepancy is apparently attributable to their failure to limit sampling to the right renal vein Since the left renal vein also drains the left ovarian or spermatic vein it should be expected to contain a higher concentration of p aminohippurate The high extraction percentage or ratio found for the right kidney indicates that the renal clearances of p-aminohippurate and diodrast are practically complete in one circulation and are excellent measures of renal blood flow in normal man During uremia this is not true

Before discussing the changes in the renal blood flow and extraction of p-aminohippurate during renal disease and uremia it

is necessary to consider the normal system Anatomically the renal circuit is unique in possessing two sets of active arterioles separated by a capillary bed, the glomeruli The efferent arterioles break up into a second capillary bed that merges into the renal veins Channels through which blood may be short circuited or shunted around the glomerular capillary beds or both capillary beds are apparently almost absent in the normal kidney (15) Certainly they are of little functional significance since procedures that alter blood flow profoundly do not affect the renal extraction of p aminohippurate and presumably therefore, the relative blood flow to functioning renal tissue (16)

Physiologically blood flow through the kidney is controlled by vascular resistance to flow which is determined largely by arteriolar cross section and is subject to chemical and nervous control The kidneys are supplied with a rich neural network, but *as yet little is known of its function Denervation apparently does* not affect blood flow to any significant degree and does not interfere with the usual response to various stimuli (17) There is reason to believe that the renal arterioles are essentially autonomous responding for the most part solely to such local factors as intravascular pressure and humoral agents

The renal vascular resistance may vary widely Exercise, emotion and the standing position excite vasoconstriction that diverts a significant volume of blood away from the kidneys (10 18) In passive orthostasis blood pools in the dependent parts of the body because muscular relaxation prevents the operation of the so called venous pumps to return blood from the limbs toward the heart As a result the volume of actively circulating blood decreases and vasoconstriction develops in response to the need for maintaining the arterial pressure and cerebral blood flow Other conditions in which the circulating blood volume is reduced *including shock chronic anemia Addison s disease and* dehydration are also associated with renal vasoconstriction Vasodilation occurs during fever of any cause in man (18) or in response to large amounts of amino acids such as glycin in the dog

(19) and presumably also in man Again these responses appear to be part of general systemic circulatory reactions in which general arteriolar vasodilation and augumentation of cardiac out put are prominent There is good reason to believe that such renal vascular adjustments occur even in the presence of renal disease (16 20)

Glomerular filtration is disturbed by renal arteriolar vasomotion because the forces governing filtration depend upon hemo dynamic relationships in the glomerular capillaries The effective filtration pressure is determined by the difference between the hydrostatic pressure driving blood through the capillaries and forcing water and its solutes through the capillary wall on the one hand and the oncotic pressure of the plasma proteins and the renal interstitial pressure resisting filtration on the other and by the area through which filtration takes place The filtration pressure is adjusted by appropriate alterations in efferent and afferent arteriolar resistances under most conditions so that the filtration rate varies little over a wide range of renal blood flow When vasoconstriction is marked however filtration may fall strikingly The relationship between renal blood flow and glo merular filtration rate has been studied intensively in the hope of assessing the relative importance of the afferent and efferent arterioles in the total renal resistance This problem remains highly controversial

That part of the total renal *plasma* flow which is filtered at the glomerulus is referred to as the filtration fraction This value in normal man averages twenty per cent and changes widely as renal plasma flow changes Since it seems reasonable that filtration equilibrium occurs in the glomerulus the filtration fraction should indicate the extent to which the plasma proteins are concentrated and also approximately the head of pressure under which blood perfuses the post glomerular vascular bed This is true because the plasma oncotic pressure determined by the protein content of the plasma equals the hydrostatic pressure at the equilibrium point and thereafter in the capillaries as long as free passage of

filtrate occurs Hence the value of the filtration fraction may be used in an analysis of arteriolar resistance Other variables, such as capillary resistance, renal interstitial pressure, and the changing viscosity of plasma are not readily subject to quantitative evaluation, however, and final conclusions regarding the major determinates of renal resistance have not been reached Homer Smith (21) suggests that efferent arteriolar resistance is of primary importance in affecting renal blood flow and in maintaining the constancy of glomerular filtration rate In this view afferent arteriolar constriction may contribute to the renal resistance in such conditions as orthostasis when the glomerular filtration rate is reduced, but otherwise it is of lesser importance Lamport (22) on the other hand, believes that both the afferent and efferent arterioles are active in establishing a relatively constant filtration rate and that afferent arteriolar activity is the more important

Regardless of the exact hemodynamic meaning of changes in the relationship between renal plasma flow and glomerular filtration rate distinctive patterns are observed in response to different stimuli Thus emotion epinephrine and various pressor drugs produce an increased filtration fraction associated with little change in the filtration rate (10 23 24) Orthostasis, shock, and chronic anemia tend to reduce both filtration rate and the filtration fraction to some extent Fever results in renal hyperemia and a depression of the filtration fraction

Likewise in renal disease certain typical functional patterns have been described In glomerulonephritis the filtration rate is reduced out of proportion to the renal plasma flow so that the filtration fraction falls (20) In essential hypertension the filtration rate remains relatively unchanged despite a reduction in blood flow causing the filtration fraction characteristically to be elevated (25) These distinctive patterns may be apparent even when renal damage is extensive and uremia has developed As a rule however in uremia there is a disappearance of the differences in patterns (20) Both plasma flow and filtration rate, as measured by clearance techniques are greatly reduced and the filtrate frac

tion tends to be elevated It seems probable however that the clearance values for renal plasma flow are invalid in uremia since the extraction ratio falls markedly This disturbance of extraction is apparent early in the course of glomerulonephritis when the clearance values may fail to reveal marked renal hyperemia and a resultant reduction of the filtration fraction (16) On the other hand extraction may remain high in the course of hypertensive disease even when marked renal damage judged by functional tests has occurred This may be interpreted as evidence in favor of the view that renal tubular damage in glomerulonephritis occurs as part of the fundamental disease process while in nephrosclerosis it is secondary to the vascular disease Thus blood continues to perfuse functionless tissue in nephritis but can perfuse only functioning parenchyma in hypertensive disease Another explana tion cannot be excluded however Oliver (15) has demonstrated that shunts develop in large numbers during the course of chronic Bright s disease It seems probable that the low extraction of p aminohippurate during uremia arises in part from the failure of some blood to traverse the entire renal circuit

It is not surprising to find that the renal blood flow as de termined by the clearance and extraction method is always re duced in uremia As the disease process progresses the vascular bed is deformed and reduced in size Fibrosis distorts the pattern of the vascular tree and by compression or angulation occludes and obliterates blood vessels Inflammatory changes in the vessel walls appearing in the course of diffuse glomerulonephritis, pyelonephritis or malignant nephrosclerosis, and the intimal prolifera tion associated with arteriolosclerosis lead to thrombosis and occlu sion The vessel walls become stiff rigid and studded with de posits of a lipoidal material As a result of these structural alter ations the capacity of the renal vascular bed is greatly reduced But vasomotor activity may also contribute to the disturbance in blood flow Uremia in chronic Bright s disease is nearly always associated with a profound anemia Dehydration and a reduction in plasma volume may develop as a result of the failure of the

kidney to conserve water Not infrequently congestive heart failure is a complicating factor All these disorders interfere with normal renal blood flow and might be expected to cause further reduction of flow in the presence of renal disease This is an important consideration since such functional disturbances are reversible and subject to therapeutic correction

Alone or in combination with renal structural defects, a derangement of renal blood flow causes renal insufficiency and uremia by interference with glomerular filtration rate and tubular activity It has been pointed out above that filtration may be disturbed by a functional imbalance of transcapillary forces but in uremia vascular and extravascular structural pathology is more important Apart from the direct influence of such structural defects it is very likely that intrarenal tissue tension may increase following obstruction to lymphatic drainage A large and complex lymphatic network drains the interstitial spaces of the kidneys Very little is known about the volume or character of renal lymph flow but it is well known that increased intrarenal pressure may seriously disturb filtration and renal blood flow The contribution of this factor to the pathology of renal function in chronic Bright s disease cannot be neglected but at present too few facts are available to permit an accurate evaluation

Glomerular Filtration Rate

Glomerular filtration is the first, and in many respects the most important step in the processing of blood by the kidney since the tubule cells even if entirely normal, are powerless to act in the absence of a filtrate on which to operate The constituents of the filtrate are handled individually by the tubules Some are reabsorbed almost completely others are increased in the filtrate by tubular excretion and some may pass down the tubules without alteration With reduction of the filtration rate, the latter tend to accumulate in the blood although this depends also upon the rate at which they enter the blood stream through the intestines or other portals

Defective filtration causes retention to a certain extent of all substances usually eliminated by the kidney although the decreased tubular reabsorption and continued active excretion by the tubules may mask this effect until filtration is very greatly reduced The volume and character of the filtrate also determine in some degree the activity of the tubules since transtubular transfer depends upon such factors as loading time of contact between filtrate and cells, and osmotic pressure of the filtrate

The Nature of the Filtrate The capillaries of the Malphigian bodies are suspended within Bowman s capsule by a mesentery like structure and sheathed by an incomplete network of cells of uncertain character the pericytes (26) Fluid must pass through the single layer of endothelial cells the *membrana propria* and the interstices of the pericytic net As judged from the chem ical structure of the filtrate and the factors determining its for mation the glomerular capillary walls comprise a semi permeable membrane

The beautiful studies carried out by Richards Walker and their co workers (27 29) have shown conclusively that the fluid leaving the glomerulus and entering the tubules is an ultrafiltrate of plasma The early work in this field was based upon studies of fluid obtained from the easily accessible glomeruli of amphibia Recently Walker in collaboration with Oliver has analyzed filtrate obtained from mammals The kidneys of guinea pigs rats and opossums were examined directly, superficial glomeruli located and punctured carefully with a tiny micropipette through which a small volume of filtrate was sampled The site of puncture was verified by careful microscopic examination Little or no protein appeared in the filtrate Other ingredients including creatinine and glucose were present in the same concentration as in the plasma and the fluid was isotonic with plasma It seems clear that the glomerular fluid in these mammals is an ultra filtrate of plasma

Other lines of evidence may be cited in support of this view Molecules larger than those of hemoglobin (molecular weight

68 000) cannot pass the glomerular filter but other smaller varieties pass easily without reference to their diverse diffusibilities solubilities, or structure (30) Compounds that are filtered and that do not traverse the tubule cells in either direction, such as glucose after phlorizination mannitol, or inulin, present identical urine plasma concentration ratios when they are determined simultaneously or at the same rate of urine flow (31) This means that each substance is concentrated to precisely the same extent in the urine and implies that each appears in the glomerular filtrate in the same concentration as in the plasma water despite the wide range of physical properties The dynamics of filtration though not entirely understood appear also to indicate the operation of filtration under pressure since urine flow ceases in experimental animals or the perfused kidney when the renal arterial pressure is reduced below what has been calculated to be the minimal filtration pressure (32)

A knowledge of the volume of filtrate formed each minute in the kidney is essential in a quantitative evaluation of tubular function Given this datum the load of any filtered material reaching the tubules for reabsorption may be calculated Likewise the amount of any substance excreted by the kidneys may be estimated by subtracting that which has been filtered, from the total amount appearing in the bladder each minute As pointed out above, an analysis of the volume of filtrate in relation to the volume of plasma flow through the kidney may yield information regarding renal hemodynamics

The Volume of Filtrate The clearance method has also been used in estimating the glomerular filtration rate (33) In this instance compounds are used that are filtered and neither excreted nor reabsorbed by the tubules The total amount appearing in the bladder urine each minute divided by the concentration in the plasma (which is equal to the concentration in the filtrate) gives the volume of filtrate (UV/P when U is the urine concentration per milliliter, V the urine flow in milliliters per minute and P the concentration per milliliter of plasma) Inulin, mannitol, and

sorbitol, have proved suitable measuring materials in man (6 34) Their clearances are identical and equal to that of glucose when phlorizination prevents the tubular reabsorption of glucose The question whether these clearance values are valid measures of filtration rate during disease is important On the basis of animal studies it appears that damage to the tubules may permit the diffusion of mannitol from the lumen into the blood (35) However even if this occurs in man the value of the clearance relative to the normal (about 130 ml per min) provides an approximate measure of filtration Moreover simultaneous determination of mannitol and inulin clearances during shock and glomerulonephritis with renal insufficiency reveals equality of the values despite differences in diffusibility of the two compounds (7, 20) Hence it seems likely that glomerular filtration rate can be measured with satisfactory accuracy in man during renal disease

The determinants of the volume of filtrate are still incompletely known The hemodynamic factors discussed above probably constitute the most important forces usually involved However in disease the area and thickness of the filter bed itself become of increasing importance in determining the rate of filtration Early in glomerulonephritis the glomeruli are the chief seat of the disease process The basement membrane is thickened capillary loops thrombosed and adhesive inflammatory exudates appear Hence as expected filtration decreases (20) This characteristic of glomerulonephritis persists throughout most of the course of the disease whereas interference with filtration appears later in nephrosclerosis and is apparently secondary in part to hemodynamic changes With progression however in every type of chronic Bright s disease the area of the filter bed shrinks as glomeruli are destroyed This process is ultimately the chief cause of reduced filtration

The possibility that a certain number of glomeruli remain inactive at any one time and constitute as it were a reserve that can be called upon to supply deficiencies arising in disease has been widely discussed (36) The idea has received support in the

discovery of alternation of glomerular activity in amphibian kidneys (27) Indirect evidence has been advanced in favor of the claim that mammalian kidneys show a similar activity since only a fraction of the glomeruli in the kidneys of rabbits are filled with hemoglobin or dyed with vital stains shortly after injection of the renal artery (37, 38) Later work (39) has cast doubt on these findings since it has been shown that failure to fill glomerular capillaries with hemoglobin or dyes may be attributed to washing out before examination or to the character of streamline flow in large vessels that may direct the dye away from large areas of the vascular bed Other evidence obtained in studies of man, based on the fact that the glucose reabsorption at high plasma levels is constant despite wide changes in renal blood flow, has been interpreted as showing continuous activity of all glomeruli and nephrons in the formation of urine in man (40) Recently direct examination of glomeruli in mammalian kidneys has failed to disclose intermittency (28) Hence, the idea of a glomerular reserve in terms of inactive glomeruli available for use during an emergency must be abandoned although the fact that the kidney is capable of handling with ease a large increase in the excretory load cannot be denied This capacity is revealed in the failure of unilateral nephrectomy to produce obvious renal insufficiency It should be noted however, that all tests of filtration rate renal blood flow and maximal tubular capacities under these circumstances reveal a diminution prior to hypertrophy of the remaining kidney proportional to the loss of tissue (41) In disease also marked destruction of parenchyma precedes the appearance of renal insufficiency and uremia But the loss of tissue is readily demonstrable by appropriate functional studies

Relation of Glomerular Dysfunction to Changes in the Urine and Plasma Composition During Uremia Before closing this section it is necessary to examine some of the manifestations of defective filtration, first in regard to the urine second (and more important from the standpoint of uremia) in regard to the plasma composition No change in filtration rate occurs inde

pendently There are always allied alterations in tubular function that exaggerate or modify its effect Thus proteinuria cylindruria, hypoproteinemia and azotemia arise largely as a result of dis ordered filtration but tubular dysfunction contributes to each

Changes in the Urine Urine flow during uremia may vary widely from marked polyuria to anuria without reference to the rate of filtration because the volume of urine is determined in the main by the extent of tubular reabsorption of water Even when filtration is reduced to an extreme degree it exceeds by a signifi cant volume the rate of urine flow This fact requires emphasis because it is often erroneously assumed that an estimate of renal function can be made from the daily output of urine

Cylindruria depends upon the rate of glomerular filtration and urine flow as well as upon the presence of relatively large amounts of protein in the tubular urine It is generally conceded that a small amount of protein may be present in normal glomerular filtrate possibly due to its passage from the capillaries through small rents or pores in the glomerular membrane If it attained (and it certainly never exceeds (42)) 25 mgm per 100 ml of filtrate theoretically it could rise to 1 63 per cent in the bladder urine after tubular reabsorption of water from 130 ml of filtrate to yield 2 ml of urine However since protein fails to appear in the urine in health it must be assumed to be reabsorbed by the tubules There is evidence that this can occur When gelatin a filtrable protein of low molecular weight is injected into animals it is found both in the tubular urine and within the cells of the proximal convoluted tubules (42 43) Vital dye tightly bound to the plasma protein also enters the cells from the tubular urine presumably as a result of the activity of reabsorptive mechanisms (44)

If protein is normally present in the glomerular filtrate it is probably filtered in amounts much less than the 32 5 mgm per minute posited above so that the appearance of proteinuria im plies augmented filtration of protein due to pathology of the glomerulus rather than defective tubular reabsorption This fact

is demonstrable in the urinary excretion of protein up to sixty grams per day following the administration of albumin concentrates to patients with chronic Bright's disease (45) Assuming a fifty per cent reduction of filtration rate in these patients such a protein excretion demands a filtrate protein concentration in excess of sixty mgm per cent

When protein is precipitated from solution within the tubules casts are formed Cast formation is enhanced by reduced filtration and/or obstruction to urine flow These factors apparently stimulate water reabsorption and increase protein concentration Although concentration is one factor responsible for the predilection for cast formation in the distal segment where tubular urine becomes hypertonic other influences are at work An increase in hydrogen ion concentration causes casts to become more abundant whereas the dispersive effect of urea and other solutes tends to counteract this effect Oliver (42) suggests that chondroitin sulphuric acid or some protein precipitating agent similar to it is secreted by tubular cells in disease He places the possible site of this activity in the intercalated cells at the junction of the distal segments and the collecting tubules In support of this hypothesis he cites the metachromasia of toluidine blue (a change in the color of the dye from blue to reddish violet in the presence of sulphuric acid complexes of large molecular size, such as chondroitin sulphuric acid) by casts

It is likely that blockage of tubules by casts contributes to the reduction of renal function in disease (15) Tubules are often dilated proximal to an obstructing plug of precipitated protein containing other material such as red cells cellular debris and amorphous precipitates of inorganic compounds Filtration ultimately ceases in the attached glomerulus and the nephron becomes inactive In time destruction of the stretched tubule occurs as its walls disrupt and its cells die

Hematuria occurs not infrequently during uremia as a result of lesions within the kidney or the urinary drainage tract Tubular destruction may be associated with local hemorrhage from which

blood in small amounts may find its way into the urine Defective glomerular membranes may permit the escape not only of large molecules but also of cellular elements from the blood The total amount of blood thus lost is very small Gross hematuria occurs very rarely during uremia and is usually the result of acute exacerbations of inflammatory renal disease or of bleeding from purpuric lesions in the mucosa of the calyces pelvis ureter or bladder The usual microscopic hematuria involves the loss of no more than a few milliliters of blood per day

Changes in Plasma Composition During uremia the *plasma protein concentration* is very variable tending usually to be somewhat below, and on occasion greatly below the normal (46 47) In the nephrotic state proteinuria and hypoproteinemia are marked and are associated with lipemia and hypercholesterolemia and massive edema At this stage azotemia and other evidences of renal insufficiency are absent but as the disease advances and uremia develops the nephrotic syndrome usually recedes This phenomenon is associated with diminished proteinuria and a rise in the plasma proteins As a rule the edema and other manifestations clear altogether when the plasma albumin level rises above 2 5 grams per cent Occasionally the nephrotic syndrome persists through the course of uremia The cause for the diminished loss of protein may be traced to the reduction in glomerular filtration rate As the filter bed shrinks the area through which protein leakage can occur is diminished

The factors governing these changes in plasma proteins are not completetly understood Even when marked the loss of protein in the urine usually does not exceed twenty grams per day an amount far below the theoretical capacity of protein synthesis in normal man (48) The fact that the plasma protein level rises only when proteinuria diminishes and tends to continue to be low even when proteinuria has virtually ceased seems to imply that protein synthesis is greatly reduced Furthermore this disturbance of protein metabolism may be attributed in part to anorexia and insufficient intake of protein A d

metabolic pool is also undoubtedly implicated Certainly the protein pool is affected (49) since protein reserves are depleted and since wasting and tissue breakdown are evident clinically It is extremely interesting that a relative increase in globulin occurs (45) Alterations in volume of total body water and of plasma water resulting from urinary loss or retention may be involved in sudden changes in protein concentration Often such shifts are inexplicable

The manifestations of a disturbance in fat metabolism *lipemia* and *hypercholesterolemia* associated with the nephrotic syndrome also tend to regress as uremia develops (50) However they may persist if hypoproteinemia and edema continue to be present Since Heymann (51) and Winkler and his co workers (52) have shown *that hyperlipemia develops following bilateral nephrectomy* or ureteral ligation it seems improbable that renal insufficiency per se corrects the derangement of fat metabolism The fact remains however that lipemia disappears and the serum lipids fall to or below normal with the onset of renal insufficiency and uremia in chronic Bright s disease, provided there is simultaneous clearing of the nephrotic syndrome

Azotemia in uremia is a result chiefly of diminished filtration All the components of the non protein nitrogen in the blood including urea amino acids, uric acid creatine creatinine and various nitrogenous compounds present in very low concentration are highly diffusible pass the glomerular membrane readily, and are then subjected to tubular action to an extent depending upon the species concerned Urea is by far the most important in terms of the contribution to the total N P N and with azotemia its position becomes even more prominent Of the others only *creatinine and uric acid increase in the blood to a significant degree*

Urea creatinine and uric acid are the end products of the metabolism of protein creatine and purine and pyrimidine bases respectively Urea can participate in no manner in further metabolic processes and must be removed from the body by renal excretion almost exclusively There is evidence (53 54) that small

amounts of creatinine and uric acid may be utilized in other activities and excreted through other portals but the greater proportion of these substances also must be removed from the body via the kidney Since the renal excretion of each depends for the most part upon filtration glomerular damage during chronic Bright s disease results in their retention and accumulation in the blood The remaining components of the N P N are relatively unaffected during uremia Amino acids comprising in health about 17 per cent of the N P N rise rarely in the blood during uremia because their plasma concentration is in the main a function of hepatic activity (55 56) the concentrations of the other ingredients of the N P N are also relatively independent of renal function

The plasma concentration of urea is determined by the balance between the rate at which urea is removed by the kidney and the rate at which it is added to the body fluids The latter is based upon the catabolism of protein and amino acids incorporated in cell structures and derived from ingested food Hence the plasma urea during uremia may change in a manner that cannot be predicted on the basis of what is known about the kidney function Urea passes the glomerular membrane readily but its clearance is less than that of mannitol or inulin signifying tubular reabsorption (57) The rate of reabsorption is closely related to the rate of urine flow increasing with oliguria and decreasing toward a minimum with a diuresis in excess of two ml per minute (a fact cited in support of the view that urea diffuses passively back to the blood through the tubule cells (57 58)) Since its rate of excretion is so largely a function of filtration it is not surprising that the urea clearance falls and the urea level increases when filtration is reduced (57 59) But a good correlation is not always apparent since the urea concentration may remain within so-called normal limits until disease is far advanced and the clearance values are depressed as much as fifty per cent Goldring and Chasis (5) stress the facts that the urea concentration is related to the clearance hyperbolically rather than directly and

that the apparent discrepancy depicted in Figure 1, is to be expected (Figure 2) Moreover, the generally accepted upper limit of normal urea concentration forty mgm per cent, is too high It is possible that a reduced intake of protein also accounts in part for levels lower than might be predicted from the urea clearance On the other hand, the negative nitrogen balance of stress and of wasting probably serves to enhance azotemia late in the disease process Indeed, infection and fever may precipitate uremia, presumably in part through this mechanism

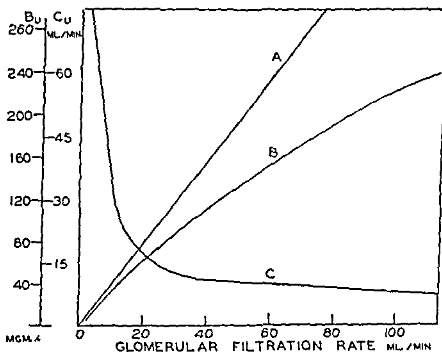


Figure 1 The relationship between glomerular filtration rate and the renal clearance and concentration of urea during *chronic Bright s disease* (based on the figures of Chasis and Smith (57)) It can be seen that the urea clearance (B) apparently falls more rapidly than the blood urea (C) rises *during the reduction of filtration rate by disease* The difference between the lines labelled A (filtration rate) and B (urea clearance) *reveals the extent* to which urea is reabsorbed from the filtrate It is interesting that the urea clearance (B) tends to approach the filtration rate (A) presumably as a result of encroachment upon obligatory water reabsorption

Creatinine increases in the plasma more slowly than urea as a rule and when present in concentrations higher than five mgm per cent bespeaks serious renal damage (60) It appears that creatinine in man at least, is excreted to some extent by the tubules (61) and the associated fall in creatinine clearance denotes tubular dysfunction as well as impaired filtration It is possible that the wasting of the body with decreased muscle mass, and reduced

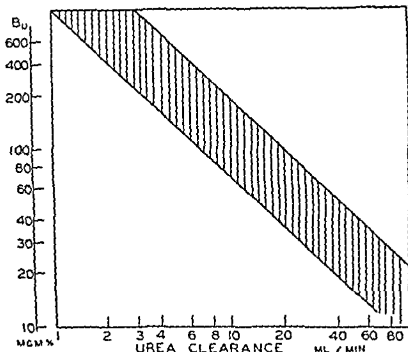


Figure 2 The relationship between the urea clearance and the blood urea plotted logarithmically (based on Goldring and Chasis (5)) It can be seen that this graph expressing the hyperbolic relation between the two variables indicates an elevation of the blood urea commensurate with the fall in urea clearance the values plotted in Figure 1 (B) falling within the shaded area This elevation of urea at intermediate values for the urea clearance is less evident in Figure 1 The belief that the upper limit of urea concentration is 40 mgm per cent is in part responsible for the erroneous conclusion that the urea level may remain normal despite a large change in its clearance Goldring and Chasis point out that the average normal blood concentration lies between 15 and 20 mgm per cent.

activity play a role in depressing creatinine formation, thus masking the retentive effect of the reduced clearance The more rapid accumulation of creatinine in the blood following urinary obstruction and anuria is believed of diagnostic value (62), although it seems likely that the difference between the two types of uremia may be a coincidental consequence of the differences in the active muscle mass and creatine metabolism

Uric acid, like urea and creatinine, appears to diffuse easily through the glomerular membrane (31) Only a small quantity is excreted in the urine, however since about 75 per cent is actively reabsorbed by the tubules It may be the first fraction of the N P N to rise in renal disease as in preeclampsia and eclampsia where decreased filtration and enhanced tubular reabsorption both appear to have a part (63) Meyer and his associates (64) have observed increments in uric acid levels early in many cases of chronic Bright s disease and they suggest that the value may be of importance in prognosis Other workers (47, 65) have since demonstrated that this phenomenon is inconstant and deceptive In general, uric acid appears to be retained in company with urea indicating that it accumulates in the plasma chiefly as a result of defective glomerular filtration Here again metabolic activities, not readily susceptible to examination, probably enter the equation

Tubular Functions

The renal tubule cells have an amazing range of functional ability They elaborate urine from glomerular filtrate by processes of selective reabsorption and excretion that are adjusted to the requirements of chemical regulation They synthesize ammonium ion to aid in preventing the escape of base in the urine They probably also manufacture certain humoral agents of importance in cardiovascular physiology Their rich content of various enzymes that split amino acids indicates their participation in nitrogen metabolism Despite their potentialities the tubule cells cannot function normally in the absence of filtrate nor can they work

efficiently when filtration is excessive This relationship between glomeruli and tubules must be taken into account in the consid eration of any tubular function

Processes of Reabsorption In view of the disparity between glomerular filtrate and urine with respect to minute volume and composition it is evident that reabsorption of most of the filtrate and its solutes occurs during passage through the tubules The processes by which reabsorption is effected are not only selective and discriminatory to a remarkable degree but also involve work in producing a urine hypotonic or hypertonic to plasma as the occasion demands (66) This means that each reabsorbed sub stance is treated more or less individually although it appears that closely related ions or molecules may be transferred by a common mechanism The processes involved have been subjected to in tensive study during the past ten years but clear cut quantitative information continues to be meager owing to the complexities of the problem

The chief source of difficulty lies in the analysis of the par ticipating and limiting factors concerned in the reabsorption of any substance In the case of non electrolytes like glucose creatine vitamin C and amino acids reabsorption is limited chiefly by the character and size of intracellular transfer systems Glucose for example is removed completely from the tubular urine as long as the total amount of glucose presented for absorption (calculated from the filtration rate and the glucose plasma level) is less than 350 mgm per minute (40) Amounts in excess of this figure are spilled in the bladder urine A constant maximal reabsorptive rate or Tm is characteristic of these substances Shannon and Fisher (67) have pointed out that this phenomenon may be ex plained on the basis of the mass action law assuming a constant quantity of some substance within the cell with which glucose combines during transfer The value of Tm then depends upon the quantity of transfer substance present and the rate at which it is liberated by decomposition to release glucose into the blood stream It is possible that the rate of combination or the relative

values of the equilibrium constants may impose further limitations upon the reabsorption of other substances, such as glycine and creatine at certain plasma levels Mutual depression of transfer maxima is exhibited by different series of similar substances when present simultaneously in the glomerular filtrate possibly because they utilize the same mechanism and compete as it were for its services Such competing series are glucose, galactose and xylose (40, 67 68) or glycine, alanine glutamic acid and arginine (69 70) Another possible explanation for this phenomenon is com petition *for available free energy This factor may be more im* portant when reabsorption is interfered with by excretory activity as in depression of glucose reabsorption by sodium p-aminohipp urate excretion (71 72) Finally it seems likely that most of these *processes are activated by enzymatic action Consequently* an en zyme inhibitor such as phlorizin may halt glucose reabsorption

In the case of electrolytes the limiting factors are far more complex In addition to the operation of finite chemical trans posal systems limitations are imposed by the demands of ionic equilibria, the influence of hydrogen ion concentration and the barrier of osmotic gradients These conditioning factors are very difficult to assess and to determine quantitatively A clearcut Tm mechanism has been described only for phosphate (73) A fail ure to find similar systems available to other ions may be ascribed to the need for unphysiologically high plasma concentrations to assure saturation and to the probability that several routes of transfer are employed in the reabsorption of such important ions as sodium chloride and bicarbonate (74) In addition endocrine activity has been found to have an important influence The hor mones of the adrenal cortex pituitary and gonads are active in promoting tubular conservation and regulation of the sodium and potassium content of the plasma (75 77)

These difficulties arise also in the case of water The reabsorp tion of water is most important in view of the quantity involved and its relation to reabsorption of other materials The larger portion of water reabsorption occurs in connection with the re

absorption of electrolytic and non electrolytic solutes This activity takes place chiefly in the proximal tubular segment as a result of the iso-osmotic withdrawal of glucose and salts accounting for approximately 100 ml of the 130 ml of glomerular filtrate formed each minute Smith (31) refers to this type of water reabsorption as obligatory in contrast to the facultative reabsorption of water in the distal segment In the latter region the urine may be concentrated by the selective reabsorption of water against an osmotic gradient a limited process requiring energy production and utilization in the performance of work The character of these processes is entirely unknown The anti diuretic hormone of the posterior pituitary is necessary for efficient operation although even in its absence concentration of the urine may occur during dehydration (76)

The Tm concept is important in this discussion because the value for Tm affords a measure of the mass of functioning tubular tissue The transfer mechanisms are apparently quite stable since values for Tm are reproducible in any individual over a long period of time and are affected chiefly by disorganization and destruction of tissue (40) Glucose is a particularly valuable substance in assaying functional tubular mass Its rate of reabsorption at any plasma level is not significantly limited by the rate of combination with the transfer substance Further it may be used not only to measure functioning reabsorptive tissue but also functioning glomeruli Obviously glucose is not available for reabsorption unless it is filtered Hence a reduction of glucose Tm will occur if either tubular or glomerular tissue is disturbed sufficiently In connection with other methods of study glucose Tm is an excellent tool for evaluating renal damage during disease

Processes of Excretion and Synthesis The thesis that the tubule cells can actively transfer certain substances from the blood into the tubular urine has been conclusively proved during the past fifteen years by studies of the renal excretion of phenol red diodrast hippuran and sodium p-aminohippurate (78) It is interesting that none of these substances occur naturally in the body Of

substances native to the blood in man only creatinine (61) and hydrogen ion (79) have been shown to appear in the bladder urine in amounts greater than can be accounted for on the basis of filtration alone But it is probable that the highly efficient tubular mechanisms of excretion subserve some such useful purpose as ridding the body of dangerously toxic foreign substances and unknown products of catabolism

The transfer systems involved in the excretion of diodrast sodium p-aminohippurate, and penicillin, exhibit limitations similar to those described for glucose, possibly dependent upon the available quantity of some transfer substance Like glucose also, diodrast heads a series of competitive compounds which show varying degrees of affinity for the transfer system Creatinine has proved more difficult to study because of the presence of interfering substances in the blood and attendent difficulties of accurate analysis but it is evident in man that the creatinine clearance ordinarily higher than the inulin or mannitol clearances, is depressed toward the latter values as the plasma level rises, owing to the saturation of a transfer mechanism Shannon (68) has shown that phlorizin will inhibit the excretory transfer of creatinine

Maximal diodrast and sodium p-aminohippurate excretory rates have proved of value in the study of the mass of functioning excretory tissue in much the same fashion as glucose Tm Excretory Tm considered in relation to renal blood flow provides information regarding the distribution of blood to the renal parenchyma When compared with glucose Tm it affords a means of assessing the relative importance of inactivation or destruction of entire nephrons as opposed to localized dysfunction of intracellular transfer systems

The tubular excretion of hydrogen ion is much more complex resembling in this respect electrolyte reabsorption since limitations are apparently imposed by factors extraneous to the mass of transfer substance itself such as the concentration and character of buffer anions, and the availability of basic and hydrogen ions

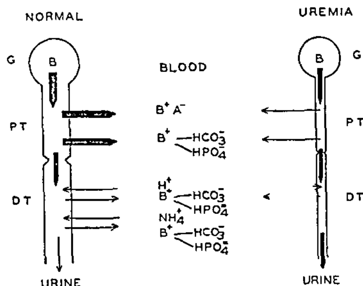


Figure 3 Renal acid base regulation in the normal and in uremia. These diagrams illustrate the basic mechanisms concerned in base conservation In the normal base (B+) is reabsorbed iso osmotically chiefly as bicarbonate and phosphate in the proximal segment (PT) This reabsorption continues in the distal segment (DT) although it is probable that little bicarbonate remains in the tubular urine at this point during acidosis In the distal segment hydrogen ion is exchanged with base and ammonium ion is manufactured for a similar purpose Very little base remains in the urine when it reaches the bladder During disease various imbalances occur Here glomerulo tubular imbalance is indicated by a smaller reduction in the size of the glomerulus (G) than in the size of the tubule Base is reabsorbed in smaller amounts by proximal segment transfer mechanisms because of impairment by disease and a relative increase in filtration of base Hence a larger quantity enters the distal segment, the larger arrow denoting the intersegmental imbalance However base salvage is still further disturbed by the absence of ammonia synthesis and possibly by diminished hydrogen ion exchange In consequence a larger total mass of base appears in the urine during uremia than in the normal

The belief that hydrogen ion is actively excreted probably in the distal tubular segment is based upon convincing evidence that the amount of hydrogen ion appearing in the filtrate during acidosis is less than the amount in the bladder urine (79) Furthermore, it has been shown that hydrogen ion excretion is markedly reduced by *sulfanilamide a well known inhibitor of carbonic* anhydrase Pitts (79) suggests that the high concentration of carbonic anhydrase in the kidney provides hydrogen ion for excretion by enhancing carbonic acid formation

Acid base regulation involves many renal activities in addition to hydrogen ion excretion (Figure 3) Base is conserved by active reabsorption apparently as bicarbonate and phosphate It seems likely that excreted hydrogen ion is exchanged for sodium in the tubular urine and excreted largely as primary phosphate, which has long been recognized as the chief constituent of urinary titrable acid (80) Pitts and Lotspeich (81) have shown that increased availability of a weak acid buffer such as phosphate is more efficacious in promoting hydrogen ion excretion than increased amounts of a somewhat stronger acid, such as creatinine But the ramifications of this complex activity are just beginning to be unravelled since the reabsorption of such anions as bicarbonate and chloride and of water is closely related to acid base excretion When excess base is present all these processes are reversed hydrogen ion is no longer excreted bicarbonate reabsorption diminishes while chloride may be removed from the tubular urine more efficiently depending upon the plasma electrolyte pattern

Another important tubular activity that aids in the conservation of base is the synthesis of ammonia Indeed during acidosis in the absence of renal disease ammonium ion may account for a saving of at least seventy per cent of reabsorbed base in contrast to twenty per cent spared by exchange with hydrogen ion and ten per cent by immediate tubular reabsorption as bicarbonate, phosphate or other salt It has recently been proved (82) that seventy per cent of urinary ammonia is derived from enzymatic breakdown of the plasma amino acid glutamine to glutamic acid and

ammonia Oxidative deamination of other amino acids accounts for the remainder (83) In general ammonia synthesis is mobilized slowly in response to the need to reduce urinary base loss and tends to outlast the need for it

Glomerulo tubular Balance Perhaps one of the most important facts brought to light through measurements of glucose Tm and glomerular filtration rate is the balance of function between glomeruli and their attached tubules Since glomeruli and tubules vary considerably in size they might be expected to vary as much in functional capacity Random distribution of tubules among the glomeruli should result in a certain proportion of imbalanced nephrons in which tubules of large capacity are attached to small glomeruli and small tubules to large glomeruli Such an imbalance would cause glycosuria to appear at relatively low blood levels of glucose due to saturation of small tubules associated with large glomeruli On the other hand it would cause glucose saturation of the kidney as a whole (Tm) to occur only after very high plasma concentrations of glucose had been attained owing to the attachment of tubules of large reabsorptive capacity to glomeruli of low filtration capacity In the normal kidney however such a disparity between the plasma glucose concentrations at which glycosuria occurs and Tm is attained has not been observed All the nephrons have been found to become saturated at the same plasma level implying a balance of glomerulo tubular capacity for handling glucose (40) It seems probable that such a balance obtains for other constituents of the filtrate In the diseased kidney this functional balance is upset

Tubular Dysfunction and Glomerulo tubular Imbalance During Uremia of Chronic Bright s Disease Since the diffuse damage of chronic Bright s disease involves every anatomical element in the kidney the resulting biochemical changes cannot usually be attributed to any single discrete dysfunction This fact has already been noted in connection with the factors underlying azotemia The disturbances of water balance and plasma electrolyte pattern are even more complex Reduced filtration withholds

water and salts from the tubules while the quantities that are filtered may be mishandled by the tubules in such a manner as to cause either excessive retention or loss The balance between renal excretion and intake or loss through extrarenal channels is also upset by disorders of metabolism and gastrointestinal function All these factors must be considered in the analysis of the changes in urine formation and plasma composition during uremia

Hyposthenuria Renal disease per se gives rise chiefly to genito-urinary symptoms and signs Proteinuria, cylindruria and hematuria have been discussed above as attributable largely to glomerular disease These changes are associated with various disorders of the volume of urine flow in the genesis of which both glomerular and tubular lesions are concerned

Polyuria with attendant changes in the relative volumes of urinary output during the day and night is a well known manifestation of chronic Bright s disease It is often referred to as compensatory in nature since it has been believed that the inability of the kidney to produce hypertonic urine (hyposthenuria) elicits a compensating increase in the volume of urine flow so that the total quantity of solids excreted does not change Although it is true that polyuria is useful in this respect it seems more likely that it is incidental rather than corrective, since polyuria, per se, may result in dangerous losses of water and salts

Hyposthenuria and polyuria develop in experimental animals following subtotal nephrectomy despite the fact that the residual tissue is structurally normal (84) Reduction of the renal arterial pressure restores the concentrating power under these circumstances, presumably by reducing the filtration pressure and thus correcting a glomerulo tubular imbalance in which *filtration* exceeds the tubular capacity to reabsorb water A similar imbalance during chronic Bright s disease may be expected to result in hyposthenuria Hyposthenuria arises also as a result of disturbances confined to the tubules An intersegmental functional balance is evident in the great differences between the volumes of water reabsorbed by proximal and distal tubular segments If the prox

imal segment fails to reabsorb its proper share of the glomerular filtrate a larger quantity of filtrate passes through the distal segment and the resultant increased rate of flow reduces the time during which water reabsorption and concentration of the filtrate can occur In consequence urine volume increases and urine concentration diminishes Finally a reduced capacity of the distal segment cells to perform work in reabsorbing water against an osmotic gradient may be implicated However it is difficult to assess this factor in the absence of data relating to the water load imposed upon these mechanisms It seems likely that in some patients the distal segment cells may be capable of performing work provided the filtrate flow is sufficiently slow Thus one occasionally sees individuals with far advanced chronic Bright s disease in uremia who excrete highly concentrated urine when other factors such as cardiac failure supervene that tend to reduce the filtration rate still more

Anuria or oliguria appear when filtration ceases altogether or becomes so small that water reabsorption is almost complete In this situation retention is the chief effect although even here extrarenal losses of water and salt may lead to dehydration and demineralization Often a so-called critical diuresis will terminate a period of oliguria or anuria This phenomenon is rare in the uremia of chronic Bright s disease and when it does occur it is usually followed by increased severity of the uremic syndrome and death It is possible that terminal collapse of tubular activity and almost complete loss of the small volume of glomerular filtrate as urine is the basis of this effect

Derangements of Plasma Electrolytes Disturbances of urine flow and of electrolyte conservation affect plasma composition in various ways Dehydration may develop independently or in company with loss of electrolytes and water and electrolytes may be retained together or separately with resultant changes in the osmotic pressure of body fluids

The plasma electrolyte pattern differs from patient to patient and at various stages during the course of uremia in the same pa

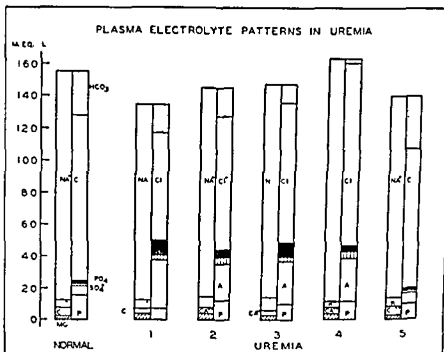


Figure 4 Various disturbances of plasma electrolyte patterns during ur emia (Diagrams 1 to 4 are based upon values given by Peters et al (85) Hypothetical values for substances not determined by these workers have been inserted for purposes of illustration Diagram 5 is based in part on values obtained in a study of a case of salt losing nephritis observed in this clinic) The normal electrolyte pattern is presented at the left of the figure

1 In this patient a severe acidosis has developed largely on account of loss of sodium Hypochloremia is marked and the place of chloride usurped by various organic acid radicals (A−) and phosphate This picture is associated with a reduction of plasma proteins below normal In this instance fluid retention as a result of hypoproteinemia may account in part for hypotonicity

2 This patient presents similar changes although the CO_2 combining power (bicarbonate) is lower than in 1 chiefly as a result of an increase in organic acids

3 Although the total base in the plasma of this case is almost normal a more severe acidosis than in 1 and 2 has developed Both phosphates and organic acids contribute to this change It should be noted that potassium is increased to a dangerously high level Calcium is greatly reduced as in patient 1 (*Continued at bottom of next page*)

tient (85) This variability, depicted graphically in Figures 4 and 5 is a consequence of the irregular involvement of the renal parenchyma by a disease process characterized by fluctuating activity Disturbances of osmoregulation of acid base adjustment and of the maintenance of balance between various ions is evident in these distortions of the chemical structure of the plasma and extracellular fluid The ions most affected are sodium chloride bicarbonate calcium and phosphate Although changes in the concentrations of the other ions do occur they are of minor importance as a rule and they will be considered at this point chiefly in relation to acid base balance

1 *Defects in Osmoregulation* The plasma may become hypertonic because water is lost or because electrolytes are retained i e with or without dehydration Both types have a similar effect upon the cells Water leaves the cells and passes into the interstitial spaces in the maintenance of the osmotic balance across cell membranes It seems likely that electrolytes move into the cell while water moves out (86) However cellular dehydration is probably minimized to some extent by protoplasmic alteration of intercellular osmotic pressure through as yet unexplored mechanisms Dehydration leads ultimately to a reduction in plasma volume and peripheral circulatory collapse As noted above further renal functional abnormality ensues intensifying the symptomatology and signs of uremia with the clinical syndrome of shock generally overshadowing the effects upon cellular physiology During hypertonicity without excessive loss of total body water the effects of the relative dehydration of cells are more prominent Sudden death due to respiratory arrest presumably

← 4 In this instance hypertonicity associated with a profound acidosis has developed An increase in sodium chloride and organic acid content is associated with a fall in potassium

5 This is an instance of salt losing nephritis with a striking reduction of both sodium and chloride In addition the bicarbonate concentration has increased and alkalosis is present

It must be emphasized that these examples illustrate but a few of the possible permutations of the electrolyte pattern seen in uremia

is renal loss of sodium The usual mechanisms by which base is conserved fail for several reasons First glomerulo-tubular imbalance with tubular diuresis shortens the time of contact between the filtrate and tubular cells in the proximal segment and, as a result sodium reabsorption is inadequate Thus a heavier load is placed upon salvaging mechanisms in the distal segment, but these are already disturbed by disease and they prove unequal to the task Ammonia production ceases (89) possibly because of enzyme inactivation Moreover, it has been found that the glutamine content decreases in the nephritic kidney (47) Hydrogen ion excretion has not been studied in this state but it seems likely that this tubular function is likewise impaired As a result of these changes sodium conservation fails and the plasma sodium level falls

Cations other than sodium may also be lost but the quantities involved are very small relative to sodium Potassium usually remains within normal limits (90) though occasionally it may show marked changes Hypopotassemia is very rare and hyperpotassemia occurs only when anuria is present or filtration reduced to an extreme degree (91) The maintenance of more or less normal potassium levels in uremia is apparently based on the relatively small mobilization of potassium for excretion Normally, reabsorption of potassium by the tubules is very efficient only a small amount escaping in the urine During disease diminished reabsorption tends to compensate for reduced filtration Most of the potassium in the body is found within cells and the possibility remains that alterations of potassium levels in uremia arise primarily from change in mobilization from cells rather than the disorder of excretion (90) Magnesium is generally elevated but to a small extent contributing little to the acid base imbalance Calcium usually falls as a result of (1) the rise of inorganic phosphate concentration and (2) a decrease in absorption from the gastrointestinal tract (i v)

Since sodium loss is associated with loss of bicarbonate and chloride there is a relative increase in strong anions The most prominent change is the reduction of bicarbonate (CO_2 combining

power) Hypochloremia is often striking because loss of chloride equivalent to that of sodium produces a greater percentile reduction in plasma chloride concentration As a rule the reduction of bicarbonate and chloride is associated with an expansion of ions derived from various organic acids These substances apparently increase in concentration because of widespread disorders in metabolism that result from the alterations in the internal environment Many patients in uremia present extreme anorexia the subsequent tissue breakdown and wasting of starvation leading to excessive mobilization of organic acids

Other anions are of relatively little importance although both sulphate (92) and phosphate increase in the blood and contribute to the acid base imbalance encroaching upon and displacing bicarbonate Both ionic species increase because of the reduction of filtration Both are normally reabsorbed but there is no evidence that increased reabsorption may be a factor in retention during uremia Sulphate ion also increases during uremia because of protein catabolism and the mobilization of excessive sulphur It is equally probable that a similar mobilization of phosphate from the large stores of organic phosphate in the cells and plasma contributes to hyperphosphatemia since it has been shown that stress causes such a mobilization due to the use of energy derived in the breakdown of energy rich organic phosphates (93) The higher concentration of phosphate in the glomerular filtrate provides a larger quantity of buffer for the excretion of hydrogen ion and probably plays a role in compensating to some extent for the failure of tubular base saving mechanisms In this manner it is possible that increased reabsorption of phosphate relative to filtration may occur but satisfactory quantitative studies of phosphate excretion during uremia have not been made

Alkalosis may occur but it is quite rare (94) This is the more surprising in view of the frequency of excessive vomiting in uremia Occasionally chloride loss in the vomitus may result in alkalosis but usually gastric acid formation is halted and insufficient chloride is lost by this route to have a serious effect

upon the chemical structure of the plasma (95) Tubular diuresis occasionally leads to excessive loss of sodium chloride and the production of a clinical state similar to the crisis of Addison s disease Thorne and his co workers (96) have shown that desoxycorticosterone is ineffective in preventing the loss of salt in these cases This rare condition may be associated with a variety of plasma electrolyte patterns, usually characterized by acidosis but alkalosis may develop

3 *Calcium Phosphorus Imbalance* The altered relationship between the plasma concentrations of calcium and inorganic phosphate require further comment since these two ions play an important role in the metabolism of bone and in neuromuscular physiology apart from their small contribution to acid base regulation Usually at some time in the course of uremia the calcium phosphorus ratio is reversed inorganic phosphates increasing in the blood while ionized calicum diminishes The reciprocal relation between the two ions is not well understood, although it is evident whenever the concentration of one is selectively altered Why phosphate increases preferentially in uremia is not clear since the renal excretion of both ions is depressed It is possible that the retention of phosphate is more rapid, leading to reciprocal depression of calcium because the diet normally contains somewhat more phosphorus than calcium because inorganic phosphate mobilization is speeded and because calcium absorption from the intestine falls Decreased calcium uptake has been attributed to failure of the gut wall to respond to vitamin D as a specific effect of uremia (97) and to precipitation of calcium as insoluble phosphate Although a few patients may respond to very large doses of vitamin D with a slight increase of calcium transfer from the gut, most do not Precipitation of calcium would also enhance the fecal excretion of phosphorus but since phosphorus is available to the plasma from the other sources the effect upon the plasma phosphorus level would be expected to be less than that upon the calcium level Calcium is available in the bone, but mobilization is slower and probably does not equal phosphate

recruitment Consequently it seems reasonable to believe that phosphate retention exceeds calcium accumulation and ultimately counteracts it insofar as plasma concentration is concerned primarily because of gastro-intestinal dysfunction that leads to loss of calcium in excess of phosphorus The resulting alteration of plasma composition sets in train a series of biochemical changes that may have serious consequences clinically

Derangements of Plasma Non electrolytes The fate of the nitrogen-containing compounds and of protein during uremia have been described above chiefly in terms of defective glomerular filtration It was evident at that point that other elements of function demanded consideration Tubular activity in reabsorption or excretion was mentioned in regard to every substance discussed There are a vast number of other organic non electrolytes in plasma concerning which little is known but that are probably subjected to filtration and possibly tubular excretion or reabsorption Among those that are recognized are the phenol derivatives creatine and creatine derivatives such as guanidine and various carbohydrates (98 101)

Very little is known about the fate of these substances during uremia or about the manner in which disturbed renal function may affect them It has been shown that both phenols and guanidine may increase in the blood and since these are very toxic great emphasis has been given this finding by those who regard uremia as a toxemia However the evidence that toxic levels are attained during uremia or that any of the manifestations of uremia can be attributed to these agents is unsatisfactory and incomplete

The plasma level of glucose is not affected in uremia because it is independent of kidney function However glycosuria may occur as a result of the depression in renal threshold probably an effect of glomerulo-tubular imbalance and the glucose tolerance may be decreased It has been suggested that the latter effect may denote a disturbance of carbohydrate metabolism (102)

Maximal Renal Tubular Reabsorptive and Excretory Capacities As renal disease progresses tubules are destroyed or

rendered impotent by glomerulo tubular imbalance or by local cellular alteration Consequently the Tm values for all substances show a progressive diminution Glucose Tm is less affected than diodrast Tm early in the course of nephrosclerosis although later the two are more or less equally disturbed (25, 40) Diodrast Tm falls in a manner roughly parallel to the reduction in filtration rate during glomerulonephritis though filtration tends to increase relative to the excretory rate in the terminal stages possibly owing to the formation of impotent tubules and/or the development of hypertension Glucose Tm has not been followed during the course of glomerulonephritis During uremia it is likely that these functional measures of tubular mass are invalidated by the severe tubular damage that may permit diffusion of tubular urine back into the blood

CLINICAL MANIFESTATIONS OF UREMIA

THE SYMPTOMATOLOGY of uremia is based primarily upon the changes in the chemical structure of body fluids resulting from the failure of renal regulation Certain symptoms and signs such as polyuria nocturia proteinuria cylindruria and rarely backache may be traced directly to renal dysfunction The remainder may be attributed to faulty systemic physiology secondary to the altered internal environment An integral part of this environment in equilibrium with and composed in part of the plasma and other body fluids is the so called metabolic pool It has recently been shown that metabolism is a continuing process (83 103 104) Stability of any structure in the body is simply evidence of a balance between constructive and disintegrative processes rather than of constancy of structural elements These balanced processes are in equilibrium with and environed by the metabolic pool any abnormality of which might be expected to produce a widespread disturbance despite the operation of a host of compensating mechanisms It seems reasonable to assume that the chemical distortions of renal insufficiency have such an effect thus producing changes in organ systems outside the kidney Toxemia secondary to renal retention of such substances as phenols or guanidine or unknown substances is often evolved as a cause of symptomatology The evidence for this point of view is not convincing Agents that have been incriminated have not been conclusively proved to appear in toxic quantities in the blood during uremia The derangement of total chemical structure of the plasma convincingly shown to be present in every case seems to provide an adequate explanation for the impressive array of symptoms It will be evident in the discussion that follows however that the intimate mechanisms by which most symptoms and signs are produced are almost entirely unknown and the possibility that toxins of some kind are operative cannot be excl

Constitutional Symptoms

Non specific complaints of weakness, easy fatiguability, dizziness, and faintness are common throughout the entire course of uremia Their origin is often difficult to trace Often they constitute the sole clinical evidence of severe renal damage One frequently sees patients who are well except for such symptoms despite renal insufficiency of a degree sufficient to produce an azotemia of more than 200 mgm per cent moderate and persistent acidosis nocturia and polyuria

The most common and obvious cause is anemia A normocytic normochromic anemia is an almost inevitable development in uremia The bone marrow may be normal or hypoplastic in appearance and in many cases maturation arrest occurs It is possible that the depression of red cell production usually attributed to toxic factors, is simply one aspect of the general metabolic disorder As renal function is progressively impaired the anemia becomes more severe and responds only to replacement of blood by transfusions or to improvement in renal function There is no evidence that increased hemolysis is important Indeed, the red cells are less fragile than normal (105, 106) Studies of iron metabolism are lacking but in view of the character of the cells and marrow iron deficiency as such seems unlikely Nonetheless this may be a factor, since iron is poorly absorbed from the gastro intestinal tract owing to precipitation as an insoluble phosphate and since there is a bleeding tendency It is interesting that achlorhydria develops as the anemia and renal insufficiency progress A relationship has been suggested (106) but it is probably coincidental rather than causal Other blood elements may also show abnormalities There is usually a moderate neutrophilic leucocytosis, although leucopenia and lymphocytopenia may occur The erythrocyte sedimentation rate is usually increased, probably as a result of the change in plasma protein pattern (106)

A bleeding tendency often contributes to the development of anemia by favoring excessive bleeding from wounds, the gastro

intestinal tract or the uterus Blood lost in hematuria is of little importance since such a small volume is involved Bleeding into the stomach, with hematemesis or into intestines with melena may be serious Menorrhagia is not uncommon and may necessitate sterilization to prevent an immediately fatal outcome Occasionally diffuse purpuric and petechial rashes appear (107 109) The cause for the bleeding diathesis of uremia is unknown In some cases a definite reduction in platelet count has been observed but in others severe bleeding may occur despite a normal thrombocyte count There is often a striking increase in capillary fragility accounting in part for purpura and easy bruisability

Changes in the skin arise not only from the bleeding tendency with purpura and petechiae and from anemia with pallor but also from local changes in pigment and water content Pigmentation is common affecting chiefly the exposed surfaces the arms face and hands It is dirty brown in hue resembling the pigmentation of chloasma but apparently not associated with increased local deposit of melanin The chemical nature of the pigment has not been studied thoroughly however It has been suggested that the deposition of retained urinary pigments may be at fault (110) Often itching is a serious and extremely annoying complication which causes the production of eczematoid lesions with secondary hyperpigmentation The etiology of itching is unknown though it is possibly related to other more prominent neuromuscular disorders One cause is found in poor hygiene with a failure to keep the skin scrupulously clean This is important in advanced uremia since the high urea content of sweat results in the deposit of urea crystals on the skin (so-called urea frost) that may prove irritating and pruritic

Edema is evident clinically by the altered character of the skin and general appearance as well as by an increase in body weight Occult edema is a frequent cause of constitutional symptomatology Fluid first accumulates in areas where the tissue tension is relatively low such as the loose skin and subcutaneous tissue about the genitalia and orbits and in the retroperitoneal spaces A

though it is often stated that edema due to renal insufficiency differs in distribution from that of cardiac failure, the apparent difference is fortuitous In decompensation a reduced vital capacity and orthopnea enforce maintenance of the upright position so that the face and upper portion of the body remains relatively free of excess fluid while the dependent portions become grossly swollen as a result of the difference in hydrostatic pressures In renal edema on the other hand orthopnea does not usually occur unless congestive heart failure supervenes As a result, facial edema is more prominent at bed rest and tends to clear sometime after assuming the upright position Renal edema is not common in uremia and when it does occur it is not usually severe Two factors operating separately or in concert may be discerned Hypoproteinemia is conducive to edema formation as a result of the imbalance of forces across capillary walls everywhere in the body Although reduced plasma protein is common in uremia, it is usually not marked, possibly as noted above, because protein loss in the urine is diminished Another factor, usually more prominent in acute diffuse glomerulonephritis but occasionally encountered duirng uremia of chronic Bright s disease is the renal retention of water and salt *Marked reduction of filtration rate*, either in absolute amounts or relative to the reabsorptive capacity of residual functioning nephrons, will result in increased volume of body fluids particularly when ingestion of water and salt continues and water loss through other portals does not occur

It was pointed out above that dehydration is the most frequent disorder of the water balance in uremia This too may give rise to lassitude weakness and other symptoms of a general constitutional disturbance It is marked clinically by drying of the mucosal surfaces by coating and crusting of the tongue by *fetor oris* and by the inelastic and doughy texture of the skin

Body weight during uremia then is a function of the effects of water retention water loss, or tissue wasting The latter occurs as a result of anorexia and predominance of catabolism over anabolism Anorexia seems chiefly important, though the second

factor is difficult to assess Wasting of all tissue occurs and the ensuing state of quasi starvation is associated with the usual metabolic disorders which contribute in turn to the chemical derangement of uremia If the diet is carefully adjusted one may stay this process for a time but even then weight loss continues in some degree The causes of anorexia are obscure though it is probable that the gastrointestinal disturbances and anemia are chiefly responsible

Gastrointestinal Symptoms

Vomiting and diarrhea are common and often the sole symptoms of uremia Nausea and vomiting usually occur in the morning As a rule vomiting is not excessive but in some instances a more serious state characterized by repeated vomiting with fluid and electrolyte loss may develop Since achlorhydria is common during uremia alkalosis does not usually develop Hydrochloric acid is not secreted in response to histamine in these patients and it has been suggested that the usually associated acidosis may be related to this phenomenon possibly through the reduction of plasma bicarbonate and diminished availability of hydrogen ion derived from carbonic acid Diarrhea is somewhat less common than vomiting and it usually appears later in the course of uremia Constipation often precedes or alternates with diarrhea The stool or vomitus may contain variable amounts of blood derived from mucosal ulcerations Cases of death due to perforation of ulcers in the duodenum or colon believed to be uremic in origin have been reported (1) The mouth partakes in the pathology of the gastrointestinal tract since ulcerative stomatitis is occasionally observed These manifestations are believed to indicate a specific inflammatory involvement of the G I tract attributable to uremia

One school of thought maintains that these signs of gastro intestinal irritation may be caused by the presence of irritating toxic substances in the bowel Urea has been implicated as such a substance It is thought to have its action indirectly through breakdown by urea splitting organisms to ammonia The ammonia

thus formed is believed to cause ulceration of the gastric or intestinal musoca and to provoke increased motility As evidence for this viewpoint Williams and Dick (111) claim that the ammonia content of the stools is increased, but it has been shown that this is not a constant finding and that ammonia is not present in sufficient amounts to cause tissue damage Jaffe and Laing (112) found slight to moderate edema of the submucosa especially involving the large intestine in 27 per cent of 136 patients dying in uremia In 53 per cent there were hemorrhages into the intestinal mucosa obviously leading to ulceration in many cases No relation between the degree and duration of azotemia was noted Hence these workers believe that the gastrointestinal manifestations of uremia arise from the hemorrhagic diathesis, rather than formation of ammonia Certainly poor hygiene and dehydration must be considered as important contributory factors Indeed, in the absence of renal insufficiency these factors may excite many changes usually attributed to uremia Moreover it is possible that the disturbances of bowel motility are related to the general neuromuscular derangement

Neuromuscular Symptomatology

Disorders of mentation and of consciousness occur commonly in uremia As a rule most patients think clearly until shortly before death, having too frequently, a lively awareness of their predicament Others become apathetic, somnolent, and sink at last into a comatose state in which they die The comatose state which generally terminates uremia may be marked by variations in depth, by convulsive seizures and by all the other manifestations of uremia Convulsions usually are a consequence of hypertension but they may occur independently in uremia

The state of the nervous system in uremia resembles that which may develop with other types of serious dehydration and metabolic disturbance, and is probably related to the changes in the local environment of nerve cells Attempts have been made to implicate various toxic substances as possible causes Harrison

and his co-workers (100) were impressed by the evidence of simultaneous excitation and depression of the nervous system They suggested that antagonistic effects of several toxic substances might produce such a picture Thus hypocalcemia would stimulate while a high plasma concentration of phenols would depress the central nervous system Although the possible activity of such agents can not be disregarded satisfactory evidence on which to base an opinion is lacking

Among the components of the internal environment that have great influence upon neuromuscular irritability are the hydrogen calcium magnesium and potassium ions Diminished concentration of the first two enhance and of the last two diminish irritability Tetanic convulsions are uncommon in uremia possibly because an augmented hydrogen ion concentration is offset by hypocalcemia However manifestations of latent tetany are common as one might expect in view of the change in concentration of all these substances Muscle cramps occur commonly and are very annoying and painful An increased intake of calcium usually brings relief The cause of fibrillary twitching of muscles in uremia remains obscure though it is evident that the tetanic tendency plays a role

Several instances of flaccid paralysis occurring in uremia associated with reduced plasma potassium concentration and changes in the electrocardiographic tracings similar to those produced in the experimental animal by hypopotassemia have been reported recently (113) Since it is believed that attacks of family periodic paralysis may be caused by sudden inexplicable withdrawal of potassium from the blood the paralytic episodes in uremia were considered to have a similar cause The apparent remission of symptoms following potassium therapy gives strong support to this view but since hypopotassemia may develop without paralysis in uremia and since family periodic paralysis may occur without hypopotassemia (114) this hypothesis must be accepted cautiously Moreover tendon reflexes are not abolished as they are in familial periodic palsy Nonetheless potassium deficit may be

at fault since potassium loss and the replacement of potassium in cells by sodium following administration of desoxycorticosterone acetate to experimental animals leads to the development of a syndrome of profound muscle weakness and apparent paralysis without loss of reflexes (115) It should be remembered that paralysis due to hysteria or other causes is as apt to develop in patients with uremia as in other individuals

Changes in Bones and Synovia

The derangement of calcium phosphorus balance may cause serious bone damage in growing children and young adults The bony changes in childhood are associated with maldevelopment retarded growth, and deformity generally referred to as renal rickets (116) This condition resembles rickets radiologically as well as clinically since decalcification swelling of the epiphyseal disks fraying of the metaphyseal margins slipped epiphyses and failure of epiphyseal closure are characteristic of both (117 118) Histologically the bony lesion in uremia is similar to that of osteitis fibrosa cystica caused by hyperparathyroidism It is claimed that about forty per cent of adults who die in uremia have microscopic bone lesions characterized by decalcification and osteoclastic activity (119) Some observers believe (120) that the osteoid seams are widened (evidence of osteomalacia or adult rickets) A further similarity to rickets is found in the poor intestinal absorption of calcium (121) However vitamin D has little or no effect in correcting this abnormality

It is well known that hyperparathyroidism causes renal damage as a result of increased urinary excretion of calcium with renal or ureteral lithiasis (122) Contrariwise, renal insufficiency associated with acidosis hyperphosphaturia and hypocalcemia has been found to evoke parathyroid hypertrophy and hyperplasia These changes differ from those of hyperparathyroidism in affecting the water clear cells rather than the chief cells (123) Since it is now generally believed that parathormone may act directly upon bone to mobilize calcium and since the bone pathology resembles

that of hyperparathyroidism (124) some investigators maintain that renal rickets should rightfully be designated renal hyper parathyroidism (125)

There is accumulating evidence in favor of the opinion that acidosis is a necessary element in the production of bone changes (126) In fact acidosis alone has been shown to produce similar pathology in animals Calcium thus is mobilized as an adjunct in correction of acid base balance as well as in response to hypocalcemia It is not known whether hyperphosphatemia or hypocalcemia are factors in evoking parathyroid hyperplasia or whether excessive production of parathormone occurs It seems likely that acidosis is of chief importance in causing bone changes in uremia and that the parathyroids play a lesser role since parathyroid hyperplasia does not resemble that of hyperparathyroidism

The mobilization of calcium from bone and the inversion of the calcium phosphorus ratio are conducive to deposits of calcium salts in regions outside the bones Metastatic calcification of subcutaneous tissues arteries pleura and peritoneum is common when these alterations are marked

Synovial tissues in addition to serving as sites for calcium salt deposit are also the seat of obscure inflammatory processes during uremia These episodes of synovitis — involving joints bursae and tendon sheaths — resemble gout in many respects since they are characterized by local swelling pain tenderness erythema heat and limitation of movement of sudden onset and rapid disappearance However there is no obvious relationship to hyper uricemia and deposits of uric acid crystals or tophi have not been observed

Cardiovascular Symptomatology

Cardiovascular involvement is usually traceable to an associated hypertension Hypertension is common in uremia and it is caused by conditions that eventually produce renal insufficiency But except insofar as hypertensive disease is a cause of renal functional impairment no causal relationship between the two conditions has been proved

In itself, however renal insufficiency may promote the development of circulatory pathology It is possible that water retention with secondary expansion of the plasma volume may induce congestive heart failure This possibility has not been thoroughly investigated and may indeed be masked by the concurrence of other causative factors Inadequate peripheral circulation is more easily discerned and occurs frequently in uremia Sooner or later dehydration reduces plasma volume and if prolonged and untreated may terminate in shock Peripheral circulatory collapse under these circumstances differs in no important particular from that seen with blood loss Fluid replacement before irreversible damage takes place is therapeutically specific

The abnormality of the internal environment is as detrimental to the activity of heart muscle as to the function of other tissues This is evident in electrocardiographic abnormalities consisting of variable changes in T waves and Q R S complexes and abnormalities of rhythm A fibrinous pericarditis develops in about one third of patients with uremia shortly before death (112) and it is a possible cause of the manifestations of myocardial disturbance that are usually attributed to uremia The extent of involvement of the pericardium varies widely at times being limited to a few patches of fibrinous tags at others affecting both visceral and parietal layers with a thick shaggy exudate, well organized with fibrous tissue producing tight and thick set adhesions Accumulation of fluid is very uncommon Clinical evidence of this process is slight Generally the diagnosis is made on the basis of an audible friction rub rarely local pain with reference to the shoulders may be observed The electrocardiographic changes are variable and non specific Pericarditis usually appears shortly before death but it may clear completely Fishberg (1) refers to one instance in his experience in which death was delayed for more than a year The cause of pericarditis is entirely unknown Bacteriologic investigation has been fruitless One can only speculate on its possible relation to other inflammatory processes of uremia such as synovitis and gastroenteritis

Anomalies of cardiac conduction may appear in uremia as a result of potassium poisoning As a rule potassium does not accumulate in the blood but with anuria or marked oliguria excretion may be so greatly reduced that retention of potassium results When the concentration exceeds ten M eq /liter serious and eventually fatal interference with myocardial activity is evident The Q R S complexes widen, the T waves are exaggerated and death occurs as a result of cardiac arrest Several instances of this phenomenon have been studied very carefully and the fact that it may occur in man during uremia of chronic Bright s disease is well documented (127, 128) Some investigators (99 100) believe that uremic blood contains other cardiotoxic substances possibly related to catechol and phenol compounds because the isolated frog heart when bathed by uremic serum shows unusual contractility which is absent when bathed by salt solution or normal sera Unfortunately these experiments have not been controlled by the use of normal sera in which the electrolyte concentrations have been changed to resemble those observed in uremia

Respiratory Symptomatology

One of the most striking manifestations of the disturbance of plasma electrolyte pattern with acidosis is hyperpnoea The characteristic breathing (Kussmaul) is deep and rapid We have seen instances in which it was the only serious complaint The lowered pH of the fluid bathing the respiratory center is apparently responsible Increased tonicity of the blood and interstitial fluid may cause dehydration of these cells and in experimental animals has been found to cause death by respiratory arrest It is possible that certain fatalities in uremia are based on this effect

Inflammatory involvement of the mucosa of the respiratory passages and larynx has been described (1) It is possible that this factor contributes to the high incidence of pulmonary infection although the loss of the cough reflex during coma is probably of equal importance

CONCLUSIONS

IT CAN BE SEEN *that uremia in chronic Bright s disease is extraordinarily* complex Beginning with dysfunction at the renal level physiological maladjustments and metabolic disorders ultimately appear everywhere in the body The agency through which these disturbances are mediated is the internal environment The fluids of the body are first affected by the inability of the kidney to regulate efficiently the chemical structure of the plasma Later the altered character of extracellular water affects intracellular fluids and intracellular activities These changes are only partially sequential since cyclic phenomena accelerate and perpetuate the disturbances of metabolism and produce further renal dysfunction It is evident in the discussion above that as the effects of Bright s disease unfold they become more and more complex, involving an increasing number of simultaneous and interlocking reactions At every stage our knowledge is inadequate but it seems probable that recognized derangements of the body fluids provide an adequate cause for the symptomatology of uremia Although unknown toxic substances may indeed be important it is necessary to maintain an attitude of cautious and friendly scepticism regarding their presence until unequivocal evidence is available

This account of the pathological physiology of uremia is necessarily incomplete not only because our information is incomplete but also because each patient presents specific problems that must be interpreted in individual rather than general terms Management is aided by a recognition of the usual changes in physiology and by a basic understanding of the normal Although specific therapeutic measures are lacking disorders of physiology may be corrected and life prolonged Since the loss of the renal regulatory mechanisms entails the loss of ability to withstand changes these patients are balanced without buffers upon a knife

edge of security from which they may be thrust at any time by neglect or by over zealous and thoughtless therapy The responsibility and the opportunity for maintaining normal physiology is in the hands of the physician

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in

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